

121

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Dear Freeman:

This is a further reaction to your letter of January 7 with its own very useful comments on my paper "Signs of Life". You may be right that the question of ultrasensitivity in detecting molecular species may have been "over engineered" in the background of some of my thinking about this question. Certainly the context of a small lander in which the gear for collecting samples of more than a few milligrams might have been prohibitively heavy was a leading factor in my earlier thinking. However, even on further reflection I think I would continue to give considerable weight, though by no means exclusive attention, to "molecular detection". Even when target material is originally quite abundant but the time we have isolated and purified the particular classes of substances in which we are most interested, we are again likely to find ourselves with vanishingly small amounts, or rather that the extent to which we can continue our analytical work is often limited by the amount of material at our disposal. This will be true then even for a fifty thousand pound lander operating in a jungle of life forms. I think we must also give considerable weight to the possibility that life is as likely to be rather sparse on Mars as it is to be extremely abundant. Now it is quite possible that some methods are unnecessarily sensitive in relation to the purposes for which they are designed, but I really can't accept the argument that a technique is too sensitive. After all, even in the contaminated column experiments to which you refer, the contamination is there whether or not the instrument used for detection is sensitive enough to tell about it, and a wise conclusion is more a matter of prudence in interpreting the results and in establishing the necessary controls than it is in blinding oneself to the sub-threshold levels of material that may be flowing through out of bounds. Good sensitive techniques will have taken account of the necessity of clean columns, instrument memories, etc. In like fashion, I would never say, and don't think I did say, that all crucial data for exobiology must be sought at the molecular level. I do retain the very strong conviction that the most decisive questions that we can ask of Martian life - apart from the possible extreme one of intelligence - do concern the molecular architecture of the system. But I think you will also note that I would recommend very strongly that all of the landing experiments which should emphasize, though not be completely dominated by, chemical analysis, should be preceded by very extensive orbital reconnaissance, which is of course generally quite unable to give detailed information at this level. If my paper really conveys such an

Dr. Freeman H. Quimby

January 28, 1965

Page 2

extreme standpoint, I would be very sorry for it, but I really think that we both understand one another's position and that the issue of emphasis on chemical versus other approaches to detection are entirely a matter of emphasis and are very difficult to deal with outside the framework of a set of concrete proposals.

I think that you and Orr might be particularly interested to hear of a remarkably clean result that Dr. Halpern has achieved in our laboratories along the lines of the gas chromatographic assay of optical activity, namely the very straightforward resolution of derivatives of D versus L amino acids. The reagent happens to be trifluoroaceto-L-prolyl, since it turned out that one of the most convenient sources of an already resolved organic reagent was itself an amino acid. We are now looking for ways in which this approach can be used on a wide variety of target material, since it has been designed so far for individual amino acids. It does look very promising indeed as a way of picking up the optical activity of submicrogram quantities of substance.

Cordially,

Joshua Lederberg
Professor of Genetics